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Procedures for the diagnosis of pneumonia in ICU patients

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Abstract. The optimal technique for diagnosing nosocomial bacterial pneumonia in critically ill patients cared for in the intensive care unit remains unclear, especially in the subgroup of patients requiring mechanical ventilation. An important advance has been the development of the protected specimen brush technique. Secretions obtained using this technique and evaluated by quantitative cultures are useful in distinguishing patients with and without pneumonia. However, this procedure has important limitations in that results are not available immediately, and in that a few false negative of false positive results may occur. Bronchoalveolar lavage has been suggested to be of value in establishing the diagnosis of pneumonia, because the cells and liquid recovered can be examined microscopically immediately after the procedure and are also suitable for quantitative culture. Microscopic identification of bacteria within cells recovered by lavage may provide a sensitive and specific means for the early and rapid diagnosis of pneumonia in this setting. The lavage technique can also be conveniently incorporated into a protocol along with quantitative culture of samples obtained using the protected specimen brush. This combination will probably improve the overall accuracy of diagnosis while allowing the administration of prompt empiric antimicrobial therapy in most patients with pneumonia.

Key words: Diagnosis – Protected specimen brush technique (PSB) – Bronchoalveolar lavage (BAL)

Nosocomial bacterial pneumonia is the third most common hospital-acquired infection and is the leading cause of death from nosocomial infection in the United States. Rates of pneumonia are considerably higher among patients in the intensive care unit compared to patients on hospital wards, and the risk of pneumonia is increased severalfold for the intubated patient undergoing mechanical ventilation [1, 2]. Despite the development of potent broad-spectrum antibiotics, fatality rates for nosocomial pneumonia remain high in the mechanically ventilated patient, ranging from 40%–80% of cases [1–3].

Rapid identification of ICU patients requiring antimicrobial therapy for treatment of nosocomial pneumonia and accurate selection of such antibiotics represent important clinical goals. Recently, two techniques have been suggested to be of value in establishing a specific diagnosis of pneumonia in critically ill patients. Firstly, the use of a double lumen catheter with a protected specimen brush (PSB) to collect uncontaminated culture specimens directly from affected areas in the lower respiratory tract, and secondly, the use of bronchoalveolar lavage (BAL), since this technique is a safe and practical method for obtaining cells and secretions from the lower respiratory tract. This review will focus on these 2 methods.

Clinical diagnosis

Conventional criteria for the diagnosis of bacterial pneumonia include new or progressing pulmonary infiltrates, fever, leukocytosis, and purulent tracheal secretions. The precise diagnosis of pneumonia in critically ill patients, however, is often difficult. Most patients have serious underlying disease, increased oropharyngeal colonization with hospital flora, and numerous reasons for elevated body temperature or leukocytosis. Chest radiographic changes consistent with pneumonia may be caused by pulmonary edema, pulmonary infarction, or atelectasis. Furthermore, microscopic evaluation and culture of tracheal secretions are frequently unrewarding, since the upper respiratory tract of most ventilated patients is colonized with potential pulmonary pathogens, whether or not deep pulmonary infection is present [4].

Studies evaluating the usefulness of clinical parameters and/or tracheal secretions in identifying ventilated patients with nosocomial pneumonia have generally been disappointing. Andrews and associates, comparing clinical criteria used for the diagnosis of pneumonia with histologic findings in the lungs of 24 ARDS patients who died during treatment found that clinical diagnoses were in error in 29% of patients [5]. Pneumonia was correctly

predicted using clinical data in 9 patients (64%) and was misdiagnosed in 5 patients (36%). The following clinical variables were present in the groups with and without pneumonia, respectively: fever, 100% vs 80%, leukocytosis or leukopenia, 100% vs 80%, pathogens in the sputum, 86% vs 70%, and asymmetric infiltrates on chest radiography, 57% vs 30%. Interestingly, only 2 of 14 patients subsequently proved to have pneumonia improved with the administration of antimicrobial agents. Similar improvement was noted in 3 of 10 patients who did not have pneumonia; the response of the patient to antibiotic treatment was therefore also an unreliable indicator of the presence or absence of bacterial infection. In a similar study from the same institution conducted by Bell and colleagues in 47 ARDS patients who died, 38% of the 35 pneumonias were also misdiagnosed [6]. Pneumonia was clinically suspected in 21 patients and confirmed histologically in 19 patients (10% false positive rate), but it was not suspected clinically in 26 patients yet it was found histologically in 16 (62% false negative rate). Likewise, in a study conducted by our group in 147 ventilated patients suspected of having lung infection, to evaluate the use of a protected specimen brush for diagnosing nosocomial pneumonia, we found that in the 24 h interval preceding the availability of the results of PSB cultures, the attending physicians were as likely to initiate or modify antibiotic treatment in patients with pneumonia as in those without pneumonia [7]. Moreover, when 16 clinical variables such as fever, leukocytosis, hypoxemia or radiologic finding were evaluated by stepwise regression analysis, no combinations were found that were useful in distinguishing patients with and without bacterial pneumonia.

As a consequence, unless further evaluation is undertaken, most patients with fever and pulmonary infiltrates are treated with one or more antibiotics. This policy based only on clinical evaluation and the results of cultures of tracheal aspirates has several potential disadvantages. Firstly, large numbers of patients who do not have bacterial pneumonia are treated with antibiotics, thus exposing them to unnecessary toxicity, delaying the diagnosis of the true etiology of the pulmonary infiltrates, and increasing hospital costs. Antibiotic therapy prior to the development of true nosocomial pneumonia influences the frequency of various types of pneumonia. Fagon et al. documented significant prior antibiotic therapy in mechanically ventilated patients with nosocomial pneumonia [3]. The incidence of *Pseudomonas* and *Acinetobacter* pneumonia was 65% in those patients with prior antibiotic therapy, compared to an incidence of only 19% in patients without prior antibiotic treatment (Fig. 1). The frequency of methicillin resistance in staphylococcal infection was increased from 33% to 100% in patients with prior antibiotic therapy. These data suggest that antibiotic therapy may not only be ineffective, but may also increase the rate of serious Gram-negative or antibiotic-resistant Gram-positive pneumonia, which have a very high mortality. Secondly, some patients with nosocomial pneumonia may not be recognized clinically, since some patients may have an atypical presentation. Finally, even if the diagnosis of pneumonia is accurate, results of cultures of tracheal aspirates could be misleading in directing the choice of antibiotics. For these reasons, we feel clinicians should pursue the diagnosis of nosocomial pneumonia more aggressively.

Bronchoscopic specimens for diagnosis

Because of the well-known inaccuracy of routine sputum cultures in diagnosing pneumonia, physicians have been researching new techniques to obtain samples from the lower respiratory tract free from contamination by upper respiratory tract bacteria. The direct needle aspiration of a pulmonary infiltrate through the chest wall is a promising older technique, recently revived [8]. Although highly specific, this technique may show low sensitivity, probably because of the small sampling area and small inoculum volume obtained for microbiological examination and the difficulty in localizing precisely the infected area [9]. In addition, this procedure carries a considerable risk of pneumothorax among ventilated patients, which prohibits its routine use. Bronchoscopy provides direct access to the lower airways for sampling bronchial and parenchymal tissue. To reach the bronchial tree, however, the bronchoscope must traverse the endotracheal tube and proximal airways where contamination is likely to occur. Therefore, distal secretions directly aspirated through the bronchoscope suction channel are frequently contaminated, thereby limiting their clinical specificity. In a study of 16 non-ventilated patients without lung infection who underwent flexible fiberoptic bronchoscopy, Bartlett et al. found that all bronchoscopic aspirates were contaminated by oropharyngeal bacteria, with an average of five bacterial species per aspirate [10]. By spraying a methylene blue marker in the posterior pharynx, they demon-

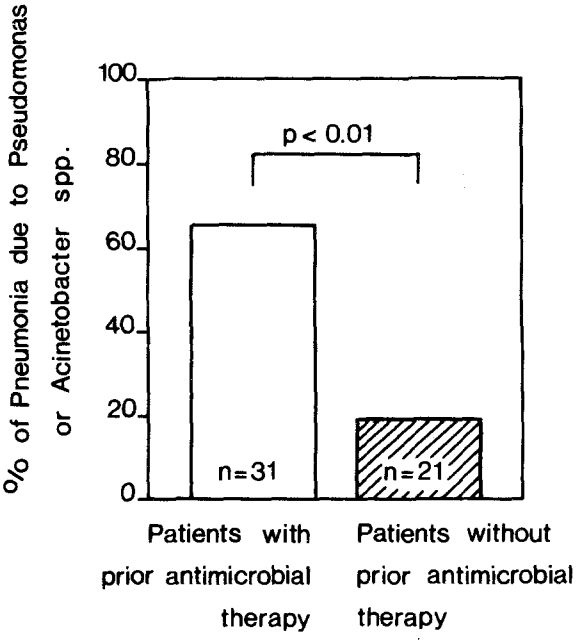

Fig. 1. Percentages of episodes of pneumonia caused by *Pseudomonas aeruginosa* or *Acinetobacter* spp. in patients receiving prior antimicrobial therapy (*open bar*) and in patients not receiving prior antibiotics (*hatched bar*) (reprinted from [7], with permission)

strated that passage of the bronchoscope resulted in the introduction of oropharyngeal contaminants into the suction channel.

The PSB technique for the diagnosis of pneumonia

Principle and methodology

To reduce contamination of lower airway aspirates collected by bronchoscopy, Wimberley and colleagues developed in the late 1970s the protected specimen brush (PSB) technique which became commercially available in 1979 [11]. This method is in fact based on the combination of four different techniques: (1) the use of fiberoptic bronchoscopy to directly sample the site of inflammation in the lung; (2) the use of a special double-catheter brush system with a distal occluding plug to reduce contamination of lower airway aspirates by flora colonizing proximal airways; (3) the use of a brush to calibrate the volume of respiratory secretions obtained; and (4) the use of a quantitative culture technique to aid in distingushing between airway colonization and serious underlying infection, with a cut-off point of 10^3 CFU/ml for making this distinction.

In an in vitro study, this catheter proved to be the most effective among seven different types of brush catheters passed through a fiberoptic bronchoscope heavily contaminated with saliva to sample a number of organisms at the distal end [8]. Since the protected specimen brush collects about 0.001 ml of secretions, the presence of $>10^3$ bacteria in the sample (1 ml) represents a concentration of at least 10^6 to 10^8 CFU/ml of respiratory secretions [12, 13]. Therefore, if one can be assured that the PSB sample was not contaminated by proximal secretions, concentrations of $>10^3$ CFU/ml in PSB specimen indicate the failure of distal defense mechanisms and significant infection of the lung.

To obtain meaningful results with the PSB technique, it is, however, very important to follow a very precise methodology, as summarized in Table 1. Three points deserve particular attention. Firstly, injection of fluids such as lidocaine through a channel contaminated with proximal secretions may introduce large numbers of bacterial contaminants into the lower airways. Thus, sedation and injection of a short-acting paralytic agent by intravenous route are recommended in ventilated patients to eliminate the need for topical anesthesia. Secondly, the distal end of the bronchoscope should be positioned close to the orifice of the bronchus draining the subsegment with new or increased infiltrates on chest radiographs. In patients with diffuse lung injury, multiple sampling should be performed in every subsegment where purulent secretions are seen. Finally, the brush should be rapidly placed after specimen collection into 1 ml of saline solution or Ringer's solution to avoid drying and rapid loss of bacteria and the sample should be rapidly submitted to the laboratory for culture.

Table 1. Methodology of the protected specimen brush technique

1. In intubated patients, sedation and a short-acting paralytic agent are recommended.
2. Do not inject lidocaine through the suction channel of the FOB and avoid suction of upper airway secretions.
3. Position the FOB close to the orifice of the bronchus draining the subsegment with new or increased infiltrate on chest radiograph.
4. Advance the PSB catheter 3 cm out of the FOB into the desired subsegment and eject the distal plug.
5. Advance the brush and wedge it into a peripheral position to sample distal secretions.
6. Retract the brush into the inner cannula, the inner into outer cannula, and remove from the FOB.
7. The distal portion of the outer and inner cannula are separately and sequentially wiped clean with 70% alcohol, cut, and discarded.
8. Advance the brush out and sever it into a container with 1 ml of saline or Ringer's solution.
9. Submit for quantitative culture within 15 min.

(Adapted from [38] with permission)

Usefulness of the PSB technique for diagnosing pneumonia

The usefulness of the PSB technique in evaluating patients receiving mechanical ventilation who are suspected of having pneumonia has been extensively investigated in both human and animal studies [7, 14–29]. However, in only four studies [14–17] was the relative cultural accuracy of the PSB method determined with an acceptable "gold" standard, i.e. in comparison both with histologic features and quantitative cultures from the same area of the lung. Moser and coworkers [14], using three different techniques (transthoracic needle aspiration, PSB, and transbronchial biopsy) in a canine model of *Streptococcus pneumoniae* pneumonia, found that the sensitivity of the PSB technique was high, ranging between 90% and 100%. Higuchi and colleagues [15] studied the diagnostic value of the PSB technique in intubated baboons with nosocomial pneumonia without previous antibiotic treatment. Of the 10 baboons with nosocomial pneumonia 7 had positive PSB cultures and no false positive results were observed. In studies evaluating the appearance of pneumonia in ventilated baboons with permeability pulmonary edema, Johanson and associates also found that quantitative cultures of PSB specimens showed a good correlation with the bacterial content of lung tissue, even if the results were inferior to those obtained with bronchoalveolar lavage [16]. On comparing the results of BAL with quantitative PSB cultures taken from the same lobe, utilizing lobar tissue cultures as the standard for comparison, BAL and the PSB techniques had a similar specificity, but BAL was a little bit more sensitive, recovering 74% of the organisms isolated from tissue, while the PSB technique identified only 41% of these species. Of the 9 bacteria present in the lung in concentration greater than 10^4 CFU/g 7 were, however, isolated by the brush (sensitivity 80%), and only micro-organisms present in low or in very low concentrations in the lung were missed by this technique [16].

To determine the operating characteristics of the PSB technique for diagnosing lung infection in patients undergoing mechanical ventilation, our group in Bichat hospital performed bronchoscopy in 26 intubated patients with respiratory failure just after their deaths, while mechanical ventilation was continued [17]. After obtain-

ing a PSB sample from the anterior segment of the left lower lung, this lung segment was removed by thoracotomy and subjected to histologic evaluation and quantitative bacterial culture. All 6 patients with pneumonia determined by histologic criteria had at least one micro-organism that grew in concentrations greater than 10^4 CFU/g on lung cultures; 4 had polymicrobial growth. Cultures of the PSB yielded 15 of the 19 bacteria present in the lung cultures and no additional organisms; and all PSB cultures had at least one micro-organism in a concentration above 10^3 CFU/ml. Twenty patients had no histologic evidence of pneumonia in the lung segment removed by thoracotomy. In the subgroup of 12 patients who received antibiotics prior to death, seven had at least one organism at a concentration $>10^3$ CFU/ml, representing a false positive rate of 58%. In the subgroup of patients who received no antibiotics, the false positive rate was only 23% and the positive predicted value was 73%. Using the cut-off point of 10^3 CFU/ml to define a positive PSB culture, no false negative results were observed.

More recently, the clinical utility of PSB has been studied by Fagon et al. in a large group of intubated patients, most ventilated for respiratory insufficiency after cardiac surgery [7]. Results of quantitative culture of the PSB showed that only 45 patients (30%) had at least one micro-organism growing above the cut-off point of 10^3 CFU/ml. The diagnosis of pneumonia was confirmed in 34 of these patients (28 by autopsy, 6 by response to treatment); pneumonia could not be accurately defined in 7 and was excluded in 4 (false positive rate, 11%). There were 102 patients who either had no growth (77 patients) or the PSB culture yielded $<10^3$ CFU/ml. None of them had bacterial pneumonia, excluded in most at autopsy (34 patients) or by recovery without antibiotic therapy. The positive predictive value of a positive culture ($\geq 10^3$ CFU/ml) was greater than 75%.

The reliability of the PSB technique in the diagnosis of lower respiratory tract infection was also studied by Baughman et al. [18] in 21 intubated and ventilated patients, including 8 patients with proven bacterial infection. Cultures of the PSB specimen from the affected lung in all 8 cases of bacterial pneumonia had one or more organisms present at >100 CFU/ml, while only one of the 13 cases of non-pneumonia had a culture from the affected area of >100 CFU/ml. The unaffected area always grew fewer organisms than the affected area, and in 16 cases there was no growth from the specimen obtained from the unaffected area.

Despite the need for interpretive caution, these studies indicate that the PSB technique offers a rather sensitive and specific approach in critically ill patients to establish the organisms in case of pneumonia and to differentiate between colonization of the upper respiratory tract and distal lung infection. When the results of the 18 studies which have evaluated the PSB technique in critically ill patients [30] for a total of 524 patients, are pooled together, the overall accuracy of this technique for diagnosing nosocomial pneumonia was high, with a sensitivity of 90% and a specificity of 94.5%.

Table 2. Potential limits and drawbacks of the PSB technique

1. Patients with diffuse lung injury
2. Patients receiving prior antimicrobial therapy
3. Risks inherent in bronchoscopy in ICU patients
4. Hospital costs
5. False positive results
6. False negative results
7. Absence of information to guide initial therapy

New developments of the PSB technique

Recently, two modifications of the PSB technique were proposed with apparently acceptable results that would further simplify the procedure and reduce costs if further studies confirm the preliminary results. The first was suggested by Torres et al. who developed a nonbronchoscopic method to perform protected brushing, using a Metras catheter without fluoroscopy through an endotracheal tube [19]. In a study of 25 ventilated patients, these authors demonstrated that the sensitivity of the non-bronchoscopic PSB and the bronchoscopic PSB were nearly similar (64% vs 71%), with a predicted value of 100% for both. The second is based on the use of a new device composed of a plugged telescoping catheter (PTC) used with or without fiberoptic bronchoscopy [28]. In a study of 78 suspected episodes of nosocomial pneumonia in 55 patients, Pham and colleagues found that this device gave similar results with the PSB technique in 74% of the cases. A major discrepancy was observed between the two techniques in only 20 episodes, including 6 false negatives of PSB in episodes of proved pneumonia, four possible false positives of PSB and 10 possible false positives of the plugged catheter. Furthermore, blinded or directed samples had similar concordance with PSB samples taken via bronchoscopy.

Potential limits and drawbacks of the PSB technique

Before implementing extensive clinical use of the PSB technique, some potential limits or drawbacks of this method should be considered (Table 2). First, a "negative" ($<10^3$ CFU/ml) result suggests only that a bacterial process is improbable in the area where sampling was performed. Obviously, a negative result could not eliminate a pneumonia involving another area of the lung. To exclude definitely a bacterial process in a ventilated patient with diffuse lung injury, the physician has to perform multiple samplings in different areas of the lung. It is also possible that erroneous false negative results might be observed with the PSB technique after topical anesthesia of the tracheobronchial tree with lidocaine through the inner channel of the bronchoscope. In our clinical experience, this type of anesthesia can be avoided in ventilated patients, providing there has been adequate analgesia previously.

While a cut-off point of 10^3 CFU/ml indicating the presence of pneumonia is well established in patients not receiving antibiotics, the culture results of PSB specimens recovered from patients receiving prior antimicrobial therapy can be difficult to interpret. As demonstrated by

ourselves and Johanson and coworkers [16, 17], the PSB technique appears to work well in cases where pneumonia develops as a superinfection in patients who have been receiving systemic (but not topical) antibiotics for several days before the appearance of the new pulmonary infiltrates, the reason being that the bacteria responsible for the new infection are then resistant to the antibiotics previously given. In contrast, the PSB technique is probably of little value in patients with a recent pulmonary infiltrate who have received new antibiotics for that reason, even for less than 24 h. In this case, a negative finding could indicate either that the patient is successfully treated for pneumonia and the bacteria are eradicated, or that he had no lung infection to begin with. These 2 different clinical situations should be clearly distinguished before interpreting a PSB result in a patient receiving prior antibiotics. In the latter situation, no conclusion concerning the presence or absence of pneumonia could be drawn if the PSB result is "negative", emphasizing the need to make every effort to obtain the PSB specimens before new antibiotics are administered. Interestingly, the only study in which the PSB technique had a sensitivity of less than 80% (59%) was a study in which the bronchoscopy was performed shortly after administration of new antibiotics [25].

Fiberoptic bronchoscopy is generally regarded as safe, based on surveys of endoscopists. The risk inherent in such an examination appears slight, even in critically ill patients requiring mechanical ventilation, although the associated occurrence of cardiac arrhythmias, hypoxemia, or bronchospasm is not unusual. A recent study conducted by our group in 107 ventilated patients has shown that fiberoptic bronchoscopy under midazolam sedation is practicable in this setting [23]. No death or cardiac arrest occurred during or within the 2 h immediately following the procedure. However, patients in the ICU are at risk of relative hypoxemia during fiberoptic bronchoscopy, even when high levels of oxygen are provided to the ventilator and gas leaks around the endoscope are minimized by a special adaptor. An average decline in mean arterial oxygen tension of 26% was observed at the end of the procedure, compared to the baseline value, and this was associated with a mild increase in $PaCO_2$. The degree of hypoxemia induced by fiberoptic bronchoscopy in this study was linked to the severity of pulmonary dysfunction and the decrease in alveolar ventilation. Clinical hypoxemia, as defined by PaO_2 lower than 60 mmHg, was more frequent in patients with ARDS and in those who "fought" the ventilator during the procedure, as shown by multivariate analysis. Careful methodic attention to the anesthetic protocol with addition of a short-acting neuromuscular blocking agent, and monitoring of patients during bronchoscopy should probably permit rapid correction and more frequent prevention of hypoxemia in this setting, and therefore should further decrease the morbidity of this procedure.

The cost of the protected specimen brush technique is commonly considered as too expensive, limiting its use. In fact, the cost of evaluation and treatment of patients in whom lung infection is suspected is probably less with the PSB technique than with a conventional strategy, since this procedure reduces the unnecessary use of antibiotics in such patients. For example, we could demonstrate in a consecutive series of 147 patients clinically suspected of having pneumonia that the actual costs of performing bronchoscopy ($78/patients), obtaining the protected brush catheter specimens ($30/patients), and processing these specimens using quantitative culture techniques ($50/patients) were less expensive after only 6 days of treatment when compared with the projected costs entailed in treating all patients clinically suspected of having infection with antibiotics [7].

Although the PSB technique has low morbidity and classifies most patients with and without pneumonia, 3 important drawbacks are still inherent in this technique. Firstly, using the most accurate threshold of 10^3 CFU/ml to separate patients with airway colonization from those with deep lung infection, a small number of false positive results may be observed [7, 17, 28]. Secondly, results of such cultures require 24–48 h, and therefore no information is available to guide initial decisions concerning the appropriateness of antimicrobial therapy and which antibiotics should be used. Finally, since the specimen brush obtains samples from only a limited area of the lung, some false negative results may be observed if proper catheter placement is not obtained [25, 26, 28]. Given the high mortality and morbidity of nosocomial pneumonia in ICU patients, even a very low ($<10\%$) rate of false negative results would be inacceptable in clinical practice. Therefore, the search for complementary techniques for diagnosing nosocomial pneumonia in this setting is warranted.

Evaluation of BAL for the diagnosis of pneumonia

The evaluation of bronchoalveolar lavage (BAL) seems to be a logical next step, since this technique has been extremely helpful in diagnosing a wide range of lung infections in immunocompromised persons. Indeed, several considerations suggest that BAL might be useful in establishing the diagnosis of bacterial pneumonia. Lavage is a safe and practical method for obtaining cells and secretions from the lower respiratory tract. The technique obtains samples from a relatively large area of the lung, and the cells and liquid recovered can be examined microscopically immediately after the procedure and are also suitable for culture using quantitative techniques.

Usefulness of quantitative culture of BAL fluid for diagnosing pneumonia

Two reports indicate that BAL employing quantitative bacteriological techniques can accurately diagnose bacterial pulmonary infections in non-ventilated patients [32, 33]. Thorpe and associates [32] performed BAL with the bronchoscope introduced either transnasally or through an endotracheal tube in a heterogenous group of 92 hospitalized patients, 15 of whom were thought to have active bacterial pneumonia. Of the 15 patients with clinically active bacterial pneumonia 13 had a BAL culture of $>10^5$ CFU/ml of BAL fluid, whereas none of the other

groups, including patients with a resolving pneumonia or chronic bronchitis, had counts of $>10^4$ CFU/ml; in most instances counts were substantially less than this. Furthermore, Gram stain of cytocentrifuged BAL fluid was positive (one or more organisms seen per 1000× field) only in those patients with an active bacterial pneumonia. In a similar study, Kahn and Jones evaluated 75 patients (most of whom were immunocompromised) by fiberoptic bronchoscopy and BAL for the presence of bacterial lower respiratory tract infection [33]. BAL specimens were cultured quantitatively for aerobic bacteria and a cell differential of the BAL cell population was obtained. In 18 "control" patients, without evidence of respiratory infection, the presence of >1% squamous epithelial cells in the BAL sample accurately predicted the presence of heavy contamination of the sample by oropharyngeal flora. In the remaining study patients with potential infection, potential pathogens were recovered in concentrations of $>10^5$ CFU/ml in 16 of 18 patients with bacterial infection (none had >1% squamous epithelial cells in their BAL sample). No patient without evidence of bacterial infection and with <1% of squamous epithelial cells had $>10^5$ CFU/ml in BAL cultures, but contamination of the lavage fluid occurred in a relatively large number (26%) of patients.

Other recent data published by Kirkpatrick and Bass also suggest that BAL may be highly contaminated by oropharyngeal bacterial flora [34]. Quantitative BAL and PSB cultures were obtained from 8 normal subjects; BAL cultures were positive in 7 of 8 subjects, while only one of 8 subjects had a positive PSB culture. It is important to note that quantitative BAL cultures did not demonstrate significant amounts of micro-organisms ($>10^3$ CFU/ml), but the study does suggest that upper airway contamination is common with BAL cultures.

The utility of BAL in nosocomial pneumonia has been also reported in ventilated animals and humans. Quantitative BAL cultures were performed by Johanson et al. in 36 mechanically ventilated baboons, 6 received no antibiotic and 29 received systemic and/or topical antibiotic treatment [16]. Cultures of tracheal secretions, BAL, PSB, and direct lung aspirates were compared to lung homogenates and histologic evidence of pneumonia. Quantitative BAL cultures correlated well with the bacterial count in the lung, provided culture results were expressed as a "bacterial index" (BI). The BI was calculated by the addition of $\log_{10}$ concentration of individual bacterial species. Only animals receiving topical antibiotic therapy had negative BAL culture and no pneumonia. In the 6 animals not receiving antibiotic therapy, BAL cultures were positive and pneumonia was found. Therefore, the utility of BAL cultures in a situation analogous to clinical airway colonization (without definite pneumonia) is not known.

Comparison of quantitative BAL cultures to PSB cultures has also been made in ventilated patients by Chastre et al. who evaluated 21 ventilated patients clinically suspected of nosocomial pneumonia because of presence of new pulmonary infiltrates and purulent tracheal aspirates [24]. Pneumonia was diagnosed in 5 patients with greater than 10^3 CFU/ml by PSB and verified by rapid cavitation of lung infiltrates or by lung histopathology. When quantitative BAL cultures were evaluated, no clear threshold separated those patients with or without pneumonia in contrast to quantitative PSB cultures. If the bacterial index suggested by Johanson et al. was used to predict the presence or absence of pneumonia, approximately 30% of patients without pneumonia would have been treated and 40% of patients with pneumonia would not have been treated.

More recently, Torres compared BAL and PSB in 34 mechanically ventilated patients [25]. Pneumonia was diagnosed only clinically. Agreement was excellent (88.5%) between BAL and PSB with respect to the type of organism recovered. Disagreement existed in only one case. However, closer examination of these data suggests that while the type of organisms recovered was similar the quantity of these organisms differed. Only 14 of 25 patients had agreement in the type and quantity of organism recovered with PSB and BAL. Conflicting results were also reported by Pugin and colleagues in a series of 28 patients requiring prolonged mechanical ventilation and presenting a high risk of developing pneumonia [35]. Similar to studies in baboons, patients with pulmonary infection (as assessed clinically) could be distinguished by a bacterial index ≥ 5 with a sensitivity of 93% and a specificity of 100%. In contrast, if the threshold of more than 10^5 CFU/ml suggested by Kahn and Jones [33] was chosen to define significant growth, 8 of 15 episodes of pulmonary infection would have remained untreated.

Several factors probably explain the apparent differences in the usefulness of lavage fluid cultures for identifying patients with pneumonia in these various studies. First, criteria used for identifying patients with pneumonia and distinguishing them from patients with only airway colonization were more or less stringent, resulting in a different classification of some patients with tracheobronchitis considered by some investigators to have deep lung infection and by others to have only proximal airways infection. Secondly, different populations of patients were included in these studies. For example, in our study in Bichat, all patients evaluated were critically ill and had fever and localized pulmonary infiltrates of recent onset. Such patients, even if pneumonia is not present, may be more likely to have significant bacterial colonization of the airways than the control groups evaluated in prior studies. Finally, it is important to note that even if the number of organisms recovered per ml of lavage fluid from patients with pneumonia was statistically higher than that recovered from patients without pneumonia, some patients with true lung infection had a low (<6) bacterial index (in particular in case of monomicrobial pneumonia, since this index is very dependent on the number of bacterial species recovered) or no bacteria recovered in high ($>10^5$ CFU/ml) concentrations from lavage fluid.

New developments of the BAL technique

Two techniques were recently proposed to circumvene the problem of contamination of BAL fluid by the flora present in proximal airways. The first one was described by

Rouby et al. [36] and is based on the use of a plugged double catheter blindly wedged into the distal airways for performing a small lavage with 20 ml of saline. The value of this new technique was tested in two groups of ICU patients. The control group was comprised of 21 patients free of any pulmonary disease throughout their stay in the ICU and the pneumonia group was comprised of 30 patients who died in the ICU with a histologically and bacteriologically proven nosocomial pneumonia. In that study, the sensitivity of a positive (using only qualitative techniques) protected lavage was 80%, whereas the specificity was 66%. Among the 43 micro-organisms isolated in the lung cultures, 74% were recovered by the lavage.

The second technique was described by Meduri and colleagues and is based on a protected transbronchoscopic balloon-tipped catheter designed to avoid exposing the instilled and aspirated BAL solution to the contaminants present in the suction lumen of the bronchoscope [29]. The samples obtained with this device in 33 patients without pneumonia and in 13 patients with pneumonia had ≤ 1 squamous epithelial cells in 91% of specimens and an absence of bacterial growth in 59% of patients without pneumonia. Using a threshold of 10^4 CFU/ml, only one false positive result and one false negative result were observed for a diagnostic sensitivity of 97% and a specificity of 92%. Two of the 49 patients who entered the study had, however, no fluid retrieved with protected BAL.

Usefulness of microscopic examination of organisms in lavage fluid

Microscopic examination of cytocentrifuged preparations obtained from BAL fluid permits us to detect very easily and rapidly the presence or absence of intracellular or extracellular bacteria in the cells and secretions lining the lower respiratory tract (Fig. 2). To further evaluate the usefulness of this type of analysis for the diagnosis of nosocomial pneumonia, our group in Bichat hospital performed BAL and PSB procedures in a series of consecutive patients suspected of having pneumonia and compared the results in 61 patients in whom a final diagnosis could be definitely established [26]. Fourteen patients had a definite diagnosis of pneumonia established by either autopsy, rapid cavitation of pulmonary infiltrates, or positive pleural culture. Among the 47 patients without pneumonia, the PSB culture showed no growth in 39 and insignificant growth in eight. In the group with pneumonia, 12 had significant growth ($> 10^3$ CFU/ml) while 2 had no growth, a 14% false negative rate. Microscopic analysis of BAL showed intracellular organisms in more than 7% of the recovered cells (86% sensitivity) and in only two of 47 without pneumonia (96% specificity). In the remaining 45 patients without lung infection, 43 had less than 2% of cells containing intracellular organism. Furthermore, in patients with pneumonia, the morphology and Gram reaction of such bacteria closely correlated with the results of PSB bacterial culture. Microscopic analysis of the BAL, therefore, may provide rapid identification of patients with pneumonia since results are immediately available, allowing early formulation of specific antimicrobial therapy that later can be modified to the results of the PSB culture and sensitivity. In addition, it is likely that the lavage procedure samples a greater area of lung tissue than the PSB. Therefore, this technique may permit us to detect some of the false negative results observed with the PSB. Combining the two techniques may then improve overall diagnostic accuracy. In this series of 61 patients, 2 of the 14 patients with pneumonia were missed by the PSB technique and by counting intracellular bacteria, resulting in a sensitivity of 87% when either technique was used alone. Since the false negative results were not from the same patients, combining the 2 techniques, the sensitivity was 100% with still a specificity of 96%. We believe therefore that microscopic examination of BAL fluid can be conveniently incorporated into a protocol along with the quantitative cultures of PSB samples. Interestingly, the usefulness of this technique was confirmed in two recent studies evaluating BAL for diagnosing lung infection [29, 35]. In each study, either the Giemsa or the Gram stain was positive in all patients with pneumonia, allowing early and accurate diagnosis of lower respiratory tract infection before the results of cultures were available.

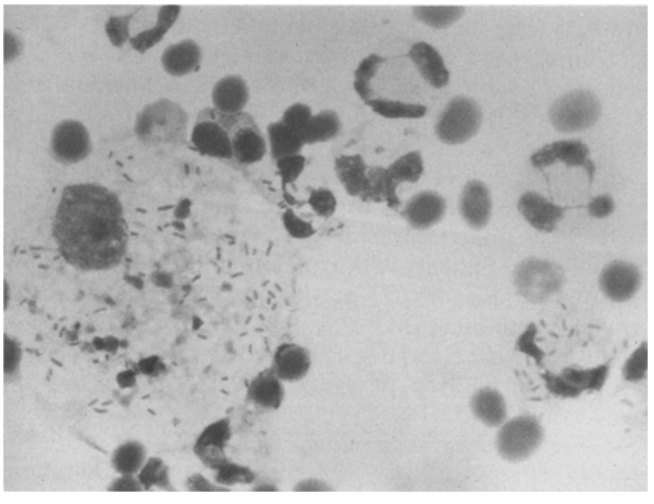

Fig. 2. Diff Quick stain of a cytocentrifuged preparation of lavage cells obtained from a patient with nosocomial pneumonia due to *Pseudomonas aeruginosa*. Note the presence of intracellular organisms within the vast majority of cells recovered by BAL

Conclusions

In conclusion, most ventilated patients without ARDS who have fever and a new infiltrate on chest radiography do not have lung infection, while pneumonia should be suspected in the febrile patient with ARDS where radiographic recognition of a new pulmonary process is difficult. We believe that decisions based only on clinical evaluation and results of cultures of tracheal aspirates result in inadequate management of a large number of patients in these settings. Even if the optimal technique for diagnosing lung infection in patients undergoing mechanical ventilation remains unclear and if several different protocols may be considered, available data suggest that a combination of PSB and BAL provides accurate diagnostic information [37]. Until further studies become available, we feel diagnostic efforts in the form of quantitative

cultures of PSB with cytologic examination of BAL fluid should be undertaken in all patients clinically suspected of having lung infection, if at all possible before new antibiotics are administered. If both diagnostic procedures are negative, empiric antibiotic therapy for nosocomial pneumonia should not be started or continued.

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